

## REMARKS

The Office Action mailed 22 October 2003, has been received and its contents carefully noted. The pending claims, claims 1-3, 5-7, 10-12, and 14-31, were rejected. By this amendment, claims 1-31 have been cancelled and claims 32-50 have been added. Support may be found in the specification and claims as originally filed. No statutory new matter has been added.

Reconsideration is respectfully requested.

### Rejection Under 35 U.S.C. § 112, second paragraph

The Examiner rejected the claims under 35 U.S.C. §112, second paragraph, as being indefinite for the various reasons set forth in the Office action.

With regard to the indefiniteness rejection of "heteroatom", Applicants have amended the claims to recite S, N, and O which are provided throughout the specification as suitable heteroatoms in ring structures. As the term "heteroatom" is no longer used, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

With regard to the indefiniteness rejection of "antimalarial", Applicants respectfully submit that the term "antimalarial" is not indefinite as it is a term commonly used by those skilled in the art to refer to various compounds known in the art that are used to treat malaria. For example, see the various references provided with the Invention Disclosure Statements submitted by Applicants.

- Schmidt, "Plasmodium Falciparum and Plasmodium Vivax Infections In The Owl Monkey (Aotus Trivirgatus)", Am. J. Trop. Med. Hyg., Vol. 27(4): pgs. 703-717, (1978).
- Milhous et al., "In Vitro Strategies for Circumventing Antimalarial Drug Resistance", Antimicrobial Agents Chemother, (1985), Vol. 27: pgs. 525-530.
- Oduola et al., "Reversal of Mefloquine Resistance with Penfluridol in Isolates of Plasmodium Falciparum from South-West Nigeria", (1993), Transactions of the Royal Society of Tropical Medicine and Hygiene, 87:81-83.
- Chulay et al., "Plasmodium Falciparum: Assessment of in Vitro Growth by [<sup>3</sup>H] Hypoxanthine Incorporation", (1983), Experimental Parasitology, 55:138-146.
- Gerena, L., et al., "Fluoxetine Hydrochloride Enhances In Vitro Susceptibility To Chloroquine In Resistant Plasmodium Falciparum", (1992) Antimicrobial Agents and Chemotherapy 36:2761-2765.
- Kyle, D.E., et al., "Plasmodium Falciparum: Modulation By Calcium Antagonist Of Resistance To Chloroquine, Desethylchloroquine, Quinine, and Quinidine In Vitro", (1990) In Vitro. Trans Royal Soc. Trop. Med. Hyg. 84:474-478.
- Desjardins, R.E., et al., "Quantitative Assessment of Antimalarial Activity In Vitro by a Semiautomated Mdilution Technique", (1979) Antimicrobial Agents Chemother 16:710-718.

- Foote, *et al.* "The Mode of Action and the Mechanism of Resistance to Antimalarial Drugs" (1994) *Acta Tropica* 56:157-171.

A few examples of antimalarials recited in the references cited above include: chloroquine, quinine, mefloquine, amodiaquin, primaquine, pyrimethamine, sulfonamides, sulfones, dihydrofolate reductase inhibitors, tetrandine, and derivatives thereof. It is important to note that those skilled in the art commonly use the term "antimalarial" to refer to compounds that show activity against *Plasmodium falciparum* and *P. vivax* which is also evidenced in the references cited above.

Further, there are numerous assays for determining whether a given compound has activity against malaria, e.g. prevent or inhibit parasitic growth, that are known in the art. See, for example, the specification, Chulay *et al.* (cited above), Desjardins *et al.* (cited above), and etc. Clearly, one may readily determine whether a given compound is an "antimalarial" according to the present invention.

Therefore, Applicants respectfully submit that the meaning of the term "antimalarial" is not indefinite. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

Applicants respectfully submit that the claims as amended obviate the remaining rejections under 35 U.S.C. 112, second paragraph. Therefore, the rejection under 35 U.S.C. 112, second paragraph, should properly be withdrawn.

#### **Rejection Under 35 U.S.C. § 112, first paragraph**

The Examiner rejected the claims under 35 U.S.C. §112, first paragraph, as being nonenabled for preventing or inhibiting malaria.

Applicants have amended the claims by deleting "preventing" and "inhibiting". Therefore, the claims are directed to "treating" malaria only and the rejection under 35 U.S.C. 112, first paragraph, should properly be withdrawn.

#### **Rejection Under 35 U.S.C. § 102(b)**

The Examiner rejected claims under 35 U.S.C. §102(b) as being anticipated by Foldeak *et al.*

Applicants have amended the claims to cover the compound set forth in claim 32, which is 10-(4-pyrrolidin-1-yl-butyl)phenothiazine. Applicants respectfully submit that nowhere do Foldeak *et al.* teach, disclose or suggest this specific specie. Applicants also submit that one skilled in the art would not immediately envision the specific specie, 10-(4-pyrrolidin-1-yl-butyl)phenothiazine, upon

reading Foldeak *et al.* because Foldeak *et al.* discloses a generic chemical formula which includes an infinite number of compounds. *See In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

Therefore, Applicants respectfully submit that claim 32 directed to 10-(4-pyrrolidin-1-yl-butyl)phenothiazine is not anticipated. Since all the claims as amended are dependent on claim 32, the rejection under 35 U.S.C. 102(b) should properly be withdrawn.

#### **Rejection Under 35 U.S.C. § 103(a)**

The Examiner rejected the claims under 35 U.S.C. §103(a) as being unpatentable over Foldeak *et al.* in view of Halt *et al.* Specifically, the Examiner deemed that Foldeak *et al.* teach substituted phenothiazine and pharmaceutical compositions for use as antiplasmids and Halt *et al.* teach the MDR activity of phenothiazine derivatives and therefore it would be obvious to modify the phenothiazine compounds of Foldeak *et al.* and Halt *et al.* to obtain the instant compounds which sensitize multidrug resistant cells to antimalarial agents.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established. Specifically, Foldeak *et al.* and Halt *et al.* disclose a chemical genus that encompasses an infinite number of compounds which may or may not have a substituted benzene ring. Nowhere do Foldeak *et al.* and Halt *et al.* disclose or suggest a phenothiazine with a 4-pyrrolidin-1-yl-butyl group attached thereto to obtain the instant compound which may be used to treat malaria or used to modulate multidrug resistance against antimalarials. Nowhere do Foldeak *et al.* or Halt *et al.* provide the requisite motivation to one of ordinary skill in the art to the select the substituents of either the genus taught by Foldeak *et al.* or Halt *et al.* to obtain the instant compound with a reasonable likelihood of success in obtaining 10-(4-pyrrolidin-1-yl-butyl)phenothiazine which exhibits antimalarial activity and anti-multidrug resistance activity. As the Examiner has not provided any logical reasoning as to why specific substituents would be selected over the infinite number of those disclosed in the prior art references in order to obtain the instantly claimed compound, it appears that the Examiner has improperly used hindsight.

The Examiner also appears to imply that since the instant compound has a phenothiazine core, the instant compound is structurally similar to the prior art compounds having a phenothiazine core and therefore the instant compound will have chemical properties similar to the prior art compounds and vice versa. Nowhere did the Examiner compare the exemplary or preferred structural formulas of the prior art compounds to the instant compound. Nowhere did the Examiner provide a reasoned analysis as to why specific substituents in Halt *et al.* would have been selected by one of ordinary skill in the art.

In fact, Applicants respectfully submit that Halt *et al.* teaches away from a phenothiazine core wherein X is H. Specifically, Example 8 shows that when X is Cl, the MDR activity is increased and Table 5 shows that the MDR activity of cis and trans compounds vary significantly. Further Applicants show in the specification at Table 3 that fractional inhibitory concentration of the instant compound is significantly increased when pyrrolidinyl is changed to piperidinyl. Therefore, although the compounds may have similar phenothiazine core structures, the differences between the side chains and substituents significantly affects the compounds' activity.

Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

The Examiner rejected the claims under 35 U.S.C. §103(a) as being unpatentable over Foldeak *et al.* in view of Olsen *et al.* Specifically, the Examiner deemed that claim 1 of Olsen *et al.* disclose the instant compound with one less  $-\text{CH}_2-$  group.

Applicants respectfully submit that the Examiner misinterpreted the scope of claim 1 and the teaching of Olsen *et al.* Specifically, claim 1 recites a caveat which states "n is 1 when m is 1 and n is 0 when m is 2". Thus, when m is 1, the ring is a pyrrolindinyl ring having a  $\text{CH}_2\text{COOH}$  or  $\text{CH}_2\text{CO-alkyl}$  chain attached. When m is 2, the ring is a piperidinyl ring with a COOH or a CO-alkyl attached. The present compound as instantly claimed is a pyrrolindinyl ring without any substituents. Additionally, nowhere do Olsen *et al.* provide experimental data or evidence that compounds belonging to the disclosed genus do indeed provide anti-insulin resistance. Without any evidence showing the activity of specific compounds belonging to the claimed genus, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art to select the instantly claimed compound, 10-(4-pyrrolidin-1-yl-butyl)phenothiazine, in order to obtain a compound that exhibits antimarial and anti-malarial drug resistance with a reasonable likelihood of success.

Therefore, Applicants respectfully submit that a *prima facie* case of obviousness has not been established and the rejection under 35 U.S.C. 103(a) should properly be withdrawn.

#### **Request for Interview**

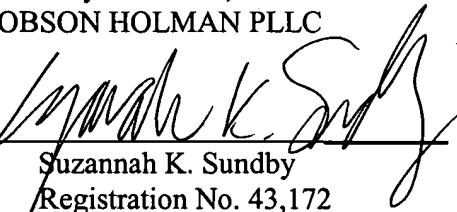
Applicants respectfully request either a telephonic or an in-person interview should there be any remaining issues.

## CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

It is not believed that extensions of time are required, beyond those that may otherwise be provided for in accompanying documents. However, in the event that additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. §1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 210-380, referencing Attorney Docket No. P66823US0 (01-06).

Respectfully submitted,  
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Date: 22 January 2003  
Atty. Docket: 12694/P66823US0